A multiscale model for pH-tactic invasion with time-varying carrying capacities

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Abstract

We propose a model for acid-mediated tumor invasion involving two different scales: the microscopic one, for the dynamics of intracellular protons and their exchange with their extracellular counterparts, and the macroscopic scale of interactions between tumor cell and normal cell populations, along with the evolution of extracellular protons. We also account for the tactic behavior of cancer cells, the latter being assumed to biase their motion according to a gradient of extracellular protons (following [2, 31] we call this pH taxis). A time dependent (and also time delayed) carrying capacity for the tumor cells in response to the effects of acidity is considered as well. The global well posedness of the resulting multiscale model is proved with a regularization and fixed point argument. Numerical simulations are performed in order to illustrate the behavior of the model.

Key words: tumor cell migration, multiscale models, pH-taxis, time-delayed carrying capacities, reaction-diffusion-taxis equations
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1 Introduction

A recent approach to cancer invasion is based on the role of the peritumoral environment in determining cancer malignancy. Gatenby & Gillies [12] suggested that biochemical events therein may drive the selection of the cancerous phenotype, and such informations can be used to conceive new therapies. Hypoxia and acidity, for instance, are factors that can trigger the progression from benign to malignant growth [10, 42]. Cancer cells upregulate certain mechanisms which allow for extrusion of excessive protons and hence acidify their surroundings. This triggers apoptosis of normal cells and thus allows the neoplastic tissue to extend into the space becoming available. Moreover, the pH was found to directly influence the metastatic potential of tumor cells [1, 28]. The mathematical modeling of acid-mediated tumor invasion seems to have begun some decades ago with the work by Gatenby & Gawlinski [9], who proposed a model involving reaction-diffusion

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equations to describe the interaction between the density of normal cells, tumor cells, and the concentration of H^+ ions produced by the latter. The well posedness of that model was investigated in [26], thereby also explicitly allowing for crowding effects (due to competition with cancer cells) in the growth of normal cells. Still in the framework of [9], traveling waves were used to characterize the aggressive action of cancer cells on their surroundings [7]. Further developments of Gatenby & Gawlinski's model involve both vascular and avascular growth of multicellular tumor spheroids, assuming rotational symmetry, for which existence and qualitative properties of the solutions were investigated [35].

The mentioned models all have a monoscale character and describe the interaction of cancer and normal cell populations, coupled with the evolution of extracellular H^+ concentration and possibly also with the concentration of matrix degrading enzymes [27]. However, this macroscale dynamics is regulated by and influences the intracellular proton dynamics [22, 37, 42]. Webb et al. [43, 44] proposed some mathematical settings for the interdependence between the activity of several membrane ion transport systems and the changes in the peritumoral space. The models involve even more biological details, like intracellular proton buffering, effects on the expression/activation of matrix metalloproteinases (MMPs) and proton removal by vasculature. Webb, Sherratt, and Fish [43] also account for the influence of alkaline intracellular pH on the growth of tumor cells, hence their model can be seen as a first step towards multiscale settings. However, the spatial dependence is essential for assessing the actual invasive behavior. This leads to more complex models, coupling the subcellular level with the macroscopic scale of populations. Some models of this new class involving both the subcellular and the population levels have been recently proposed and analyzed [29, 30, 36, 39]. A multiscale setting addressing acid-mediated tumor invasion has been presented in [17]; it also accounts for stochasticity, which is a relevant feature inherent to many biological processes occurring on all modeling levels and in particular, it seems to greatly influence subcellular dynamics and individual cell behavior [8, 14, 38]. Further multiscale settings concerning tumor cell migration -so far, however, not necessarily in connection with acidosis- take into account more modeling levels and allow for a relatively detailed description of processes taking place on the mesoscale, i.e., on the rank of individual cells and their interactions with their environment [3, 6, 19, 24].

Here we propose a multiscale model for acid-mediated cancer invasion, to be developed in Section 2 and analyzed w.r.t. global well posedness in Section 3. We present some numerical simulations in Section 4 to illustrate its performance and eventually give in Section 5 a short discussion of the results.

2 The model

We denote by $c(x,t)$ the density of cancer cells, by $n(x,t)$ the density of normal cells, and by $h(x,t)$ and $y(x,t)$ the concentrations of extracellular and intracellular protons, respectively.

2.1 Subcellular dynamics

Glycolysis is a metabolic pathway for rather inefficient energy production and normally used by cells under hypoxic conditions. Nevertheless, cancer cells consistently rely on the glucose metabolism even in normoxic conditions. The high glycolytic rate of neoplastic tissues is clinically used to diagnose and assess (via positron emission tomography, shortly

PET) tumor responses to treatment [11]. Cancer cells seem to use this aerobic glycolytic phenotype for invasion and metastasis, as -unlike normal cells- they are able to develop resistance against acid-induced toxicity. Environmental acidosis has been found to be directly related to enhanced tumor proliferation [25] and regulating angiogenesis [18]. The proton dynamics inside and outside tumor cells is controlled by a plethora of processes. Relying on the facts in [4, 44] and following [17], we describe the intracellular proton dynamics with the aid of the equation

$$\frac{dy}{dt} = -R(y,h) - \alpha y + g(c), \tag{2.1}$$

where $R(y,h)$ denotes the decay term for intracellular H^+ due to membrane transporters (e.g., NDCBE, NHE, and AE) [1], production by aerobic glycolysis (possibly depending on microenvironmental vascularization), and buffering by organelles. It describes a (saturated) growth with respect to the concentration y of intracellular protons and decay with respect to the extracellular proton concentration h and takes in the nondimensionalized model the form given in (2.6) below. The coefficient α in (2.1) denotes some decay constant, and $g(c)$ represents a source term due to the production (with saturation) by cancer cells. Observe that (2.1) is an ordinary differential equation (ODE), the variable x denoting the position of a cell having the intracellular proton concentration $y(x,t)$ and being seen as a parameter in that ODE.

2.2 Extracellular proton concentration

In order to maintain an advantageous intracellular pH, cancer cells upregulate proton extrusion through membrane transporters, leading to acidosis of the tumor environment. The concentration of extracellular protons h is a macroscopic quantity explicitly depending on time and position. It is produced the same way the intracellular protons decay by transport through the cell membrane and it diffuses through the extracellular space with a diffusion constant D_h:

$$\partial_t h = D_h \Delta h + R(y,h) \tag{2.2}$$

2.3 Cell dynamics on the macroscale

On the population level we are interested in the dynamics of tumor cells in interdependence with the normal cells and under the influence of proton concentrations. The evolution of cancer cell density is characterized by nonlinear diffusion, with the diffusion coefficient depending on the solution, more precisely inversely proportional to the interactions between cancer and normal cells, as these are slowing down the diffusivity. Furthermore, we assume the tumor cells to biase their motion in response to a gradient of extracellular protons and call this behavior pH-taxis. The notion has been firstly proposed in the context of bacteria avoiding acidic regions (hence the protons playing the role of a chemorepellent) [20] and more recently also in reference to motility of cancer cells, the latter being enhanced in the direction of extracellular pH gradient [2, 31]. The pH-tactic sensitivity function $f(h,c)$ (a concrete choice of which is proposed in (2.6) below) is nonlinearly depending on the tumor cell density and the interaction of cancer cells with extracellular protons. The tumor cell proliferation is modeled with a logistic growth with crowding. Thereby, the carrying capacity K_c of cancer cells depends on the extracellular proton concentration to

[1] NDCBE (Na^+ dependent Cl^--HCO_3^- exchanger), NHE (Na^+ and H^+ exchanger) and AE (Cl^--HCO_3^- or *a*nion *e*xchanger) are specific transporters present on the cell membrane.

stress out that the cancer cells are allowed to infer an enhanced growth due to more space becoming available through normal cell killing by acidity. However, at the same time the tumor cell density cannot exceed a certain threshold, according to the acidity level: a too acidic environment is baneful even for cancer cells. The time delay expresses the fact that their adaptation of the carrying capacity to the acidosis in the peritumoral region is not instantaneous. The proliferation rate $\mu_c(y)$ depends on the intracellular proton concentration. Indeed, malignant cells whose intracellular medium gets alkalinized were found to exhibit enhanced proliferation [5, 16, 46], which motivates the choice of μ_c in (2.6).
The normal cell dynamics is much easier to describe: normal tissue is not diffusing, it is only degraded by the environmental acidity (i.e., by the action of extracellular protons) and normal cell proliferation is supposed to be well enough described by logistic growth with crowding, also against tumor cells. The carrying capacity of the latter is still depending on the acidity, but now no longer needs to infer a time lag, as the focus is on the proliferation of normal cells.
Altogether, our multiscale model for acid-mediated tumor invasion takes the following form:

$$\begin{cases} \partial_t c = \nabla \cdot (\varphi(c,n)\nabla c) - \nabla \cdot (f(h,c)\nabla h) \\ \qquad +\mu_c(y)c\left(1 - \frac{c}{K_c(h(\cdot,t-\tau))} - \eta_1 \frac{n}{K_n}\right) & \text{in } \Omega \times (0,T), \\ \partial_t n = -\delta_n hn + \mu_n n\left(1 - \eta_2 \frac{c}{K_c(h(\cdot,t))} - \frac{n}{K_n}\right) & \text{in } \Omega \times (0,T), \\ \partial_t h = D_h \Delta h + R(y,h) & \text{in } \Omega \times (0,T), \\ \partial_t y = -R(y,h) - \alpha y + g(c) & \text{in } \Omega \times (0,T), \end{cases} \tag{2.3}$$

where $\Omega \subset \mathbb{R}^N$ is a bounded domain with smooth boundary and $N \leq 3$. Denoting by ν the outward unit normal on $\partial\Omega$, we further endow (2.3) with the boundary conditions

$$\partial_\nu c = \partial_\nu h = 0 \qquad \text{on } \partial\Omega \times (0,T) \tag{2.4}$$

and initial conditions

$$\begin{aligned} c(x,0) = c_0(x), \quad n(x,0) = n_0(x), \quad y(x,0) = y_0(x) \qquad & \text{for } x \in \Omega, \\ h(x,t) = h_0(x,t) \qquad & \text{for } x \in \Omega,\ t \in [-\tau, 0]. \end{aligned} \tag{2.5}$$

For the coefficient functions involved in (2.3), we propose

$$\begin{aligned} &\varphi(c,n) := \tfrac{D_c}{1+\frac{cn}{C_0 K_n}}, \qquad f(h,c) := \tfrac{Mc}{1+\frac{ch}{C_0 H_0}}, \qquad \mu_c(y) := \tfrac{\kappa_1}{1+\frac{y}{Y_0}}, \\ &K_c(h) := \tfrac{C_0+bh}{1+dh^2}, \qquad g(c) := \tfrac{\rho c}{1+\frac{c}{C_0}}, \qquad R(y,h) := \frac{\gamma_h y}{1+\frac{y^2}{Y_0^2}+\alpha_h h^2} - \frac{\beta_h h}{1+\frac{y^2}{Y_0^2}} \end{aligned} \tag{2.6}$$

and assume that all the constants in (2.3) and (2.6) are positive along with $\eta_1, \eta_2 \in (0,1)$.

3 Global existence

In order to prove the existence of a global weak solution to (2.3), let

$$\begin{gathered} \varphi, f, R \in C^1([0,\infty)^2), \quad \mu_c, K_c, g \in C^1([0,\infty)) \text{ such that } g \in L^\infty((0,\infty)) \\ \text{and} \quad g \geq 0,\ \mu_c > 0,\ K_c > 0 \quad \text{on } [0,\infty). \end{gathered} \tag{3.1}$$

Moreover, we assume that there exist $H_0, Y_0 \in (0,\infty)$ such that

$$\begin{gathered} R(y,0) \geq 0,\ R(y,H_0) \leq 0 \quad \text{for all } y \in [0,Y_0], \quad R(0,h) \leq 0 \quad \text{for all } h \in [0,H_0], \\ -R(Y_0,h) - \alpha Y_0 + \|g\|_{L^\infty((0,\infty))} \leq 0 \quad \text{for all } h \in [0,H_0]. \end{gathered} \tag{3.2}$$

H_0 and Y_0 are upper bounds for the concentrations of the extra- and intracellular protons, respectively. As R describes the effect of the proton exchange between the interior of the cancer cell and its environment, e.g. the first two conditions in (3.2) mean that there is no proton transport into the tumor cell if there are no extracellular protons, while protons cannot leave the cell if the extracellular proton concentration is at its maximal value.
With H_0 and Y_0 as defined above, we further assume that there exist positive constants C_1 and C_2 such that

$$0 \le f(h,c) \le C_1(1+c), \quad \frac{C_2}{1+c} \le \varphi(c,n) \le C_1 \ \ \forall (c,n,h) \in [0,\infty)\times[0,K_n]\times[0,H_0], \tag{3.3}$$

and that for any $a \in (0,H_0)$ there is $C_a > 0$ such that

$$f(h,c) \le C_a \quad \text{for all } (c,h) \in [0,\infty) \times [a,H_0]. \tag{3.4}$$

Observe that the functions given in (2.6) satisfy (3.1)-(3.4). Concerning the initial data suppose that

$$\begin{gathered} c_0, n_0, y_0 \in C^0(\bar\Omega), \quad h_0 \in C^0([-\tau,0]; W^{1,q}(\Omega)), \\ c_0 \ge 0, \quad 0 \le n_0 \le K_n, \quad 0 \le y_0 \le Y_0 \quad \text{in } \bar\Omega, \quad \delta \le h_0 \le H_0 \quad \text{in } \bar\Omega \times [-\tau,0]. \end{gathered} \tag{3.5}$$

with some $q \in (N+2,\infty)$ and $\delta > 0$. The following solution concept will be appropriate.

Definition 3.1 *Let $T \in (0,\infty)$. A weak solution to* (2.3)-(2.5) *consists of nonnegative functions*

$$\begin{aligned} &c \in L^\infty(\Omega \times (0,T)) \cap L^2((0,T); W^{1,2}(\Omega)), \quad n, y \in L^\infty(\Omega \times (0,T)), \\ &h \in L^\infty(\Omega \times (-\tau,T)) \cap L^2((0,T); W^{1,2}(\Omega)) \end{aligned}$$

which satisfy for all $\psi \in C_0^\infty(\bar\Omega \times [0,T))$ the equations

$$\begin{aligned} -\int_0^T\int_\Omega c\partial_t\psi - \int_\Omega c_0\psi(\cdot,0) &= -\int_0^T\int_\Omega \varphi(c,n)\nabla c\cdot\nabla\psi + \int_0^T\int_\Omega f(h,c)\nabla h\cdot\nabla\psi \\ &\quad + \int_0^T\int_\Omega \mu_c(y)c\left(1 - \frac{c}{K_c(h(\cdot,t-\tau))} - \eta_1\frac{n}{K_n}\right)\psi, \end{aligned} \tag{3.6}$$

$$-\int_0^T\int_\Omega n\partial_t\psi - \int_\Omega n_0\psi(\cdot,0) = \int_0^T\int_\Omega \left(-\delta_n hn + \mu_n n\left(1 - \frac{\eta_2 c}{K_c(h)} - \frac{n}{K_n}\right)\right)\psi, \tag{3.7}$$

$$-\int_0^T\int_\Omega h\partial_t\psi - \int_\Omega h_0\psi(\cdot,0) = -D_h\int_0^T\int_\Omega \nabla h\cdot\nabla\psi + \int_0^T\int_\Omega R(y,h)\psi, \tag{3.8}$$

$$-\int_0^T\int_\Omega y\partial_t\psi - \int_\Omega y_0\psi(\cdot,0) = \int_0^T\int_\Omega (-R(y,h) - \alpha y + g(c))\,\psi. \tag{3.9}$$

If (c,n,h,y) is a weak solution to (2.3)-(2.5) *for all $T \in (0,\infty)$, then we call it a global weak solution to* (2.3)-(2.5).

Now we state the main result of this section which establishes the existence of a global weak solution.

Theorem 3.2 *Let $\Omega \subset \mathbb{R}^N$ be a bounded domain with smooth boundary and $N \in \mathbb{N}$ and assume that* (3.1)-(3.5) *are fulfilled. Then there exists a global weak solution to* (2.3)-(2.5) *in the sense of Definition 3.1 satisfying*

$$\begin{gathered} c \in L^\infty_{loc}(\bar\Omega \times [0,\infty)), \quad 0 \le n \le K_n \quad \text{and} \quad 0 \le y \le Y_0 \quad \text{in } \Omega \times (0,\infty), \\ h \in L^\infty((0,\infty); W^{1,q}(\Omega)), \quad 0 \le h \le H_0 \quad \text{in } \Omega \times (-\tau,\infty). \end{gathered} \tag{3.10}$$

If in addition $c_0 \in C^\beta(\bar\Omega)$ is satisfied with some $\beta \in (\frac{1}{N+2}, 1)$, then there is a unique global weak solution within the class of functions satisfying the conditions of Definition 3.1 and $h \in L^r_{loc}([0,\infty); W^{1,r}(\Omega))$ for some $r > N+2$.

In order to prove this result, we use the following regularized problems for $\varepsilon \in (0,1)$:

$$\begin{cases} \partial_t c_\varepsilon = \nabla \cdot (\varphi_\varepsilon(c_\varepsilon, n_\varepsilon)\nabla c_\varepsilon) - \nabla \cdot (f_\varepsilon(h_\varepsilon, c_\varepsilon)\nabla h_\varepsilon) \\ \qquad\qquad + \mu_c(y_\varepsilon) c_\varepsilon \left(1 - \frac{c_\varepsilon}{K_c(h_\varepsilon(\cdot, t-\tau))} - \eta_1 \frac{n_\varepsilon}{K_n}\right) \quad \text{in } \Omega \times (0, T_\varepsilon), \\ \partial_t n_\varepsilon = -\delta_n h_\varepsilon n_\varepsilon + \mu_n n_\varepsilon \left(1 - \eta_2 \frac{c_\varepsilon}{K_{c\varepsilon}(h_\varepsilon(\cdot,t))} - \frac{n_\varepsilon}{K_n}\right) \quad \text{in } \Omega \times (0, T_\varepsilon), \\ \partial_t h_\varepsilon = D_h \Delta h_\varepsilon + R(y_\varepsilon, h_\varepsilon) \quad \text{in } \Omega \times (0, T_\varepsilon), \\ \partial_t y_\varepsilon = -R(y_\varepsilon, h_\varepsilon) - \alpha y_\varepsilon + g(c_\varepsilon) \quad \text{in } \Omega \times (0, T_\varepsilon), \\ \partial_\nu c_\varepsilon = \partial_\nu h_\varepsilon = 0 \qquad \text{on } \partial\Omega \times (0, T_\varepsilon), \\ c_\varepsilon(x,0) = c_{0\varepsilon}(x), \quad n_\varepsilon(x,0) = n_{0\varepsilon}(x), \quad y_\varepsilon(x,0) = y_{0\varepsilon}(x) \quad \text{for } x \in \Omega, \\ h_\varepsilon(x,t) = h_{0\varepsilon}(x,t) \quad \text{for } x \in \Omega,\ t \in [-\tau, 0]. \end{cases} \tag{3.11}$$

Here, we choose families of functions $c_{0\varepsilon}$, $n_{0\varepsilon}$, $h_{0\varepsilon}$, $y_{0\varepsilon}$, φ_ε and f_ε, $\varepsilon \in (0,1)$, satisfying

$$\begin{gathered} c_{0\varepsilon}, n_{0\varepsilon}, y_{0\varepsilon} \in C^3(\bar\Omega), \quad h_{0\varepsilon} \in C^3(\bar\Omega \times [-\tau, 0]), \quad \tfrac{\delta}{2} \le h_{0\varepsilon} \le H_0 \quad \text{in } \bar\Omega \times [-\tau, 0], \\ c_{0\varepsilon} \ge 0, \quad 0 \le n_{0\varepsilon} \le K_n, \quad 0 \le y_{0\varepsilon} \le Y_0 \quad \text{in } \bar\Omega, \\ \partial_\nu c_{0\varepsilon} = \partial_\nu h_{0\varepsilon} = 0 \qquad \text{on } \partial\Omega, \\ \varphi_\varepsilon \in C^3([0,\infty)^2) \cap W^{2,\infty}([0,\infty) \times [0, K_n]), \quad \max\{\varepsilon, \tfrac{\tilde C_2}{1+c}\} \le \varphi_\varepsilon(c,n) \le \tilde C_1 \\ f_\varepsilon \in C^3([0,\infty)^2) \cap W^{2,\infty}([0, H_0] \times [0,\infty)), \quad 0 \le f_\varepsilon(h,c) \le \tilde C_1(1+c), \\ K_{c\varepsilon} \in C^3([0,\infty)), \quad 0 < a_2 \le K_{c\varepsilon}(h) \le a_1 \end{gathered} \tag{3.12}$$

with positive constants $\tilde C_1$, $\tilde C_2$, a_1, a_2 for all $(c,n,h) \in [0,\infty) \times [0, K_n] \times [0, H_0]$ and any $\varepsilon \in (0,1)$ as well as

$$\begin{gathered} c_{0\varepsilon} \to c_0 \quad \text{and} \quad n_{0\varepsilon} \to n_0 \quad \text{and} \quad y_{0\varepsilon} \to y_0 \quad \text{in } C^0(\bar\Omega) \\ h_{0\varepsilon} \to h_0 \quad \text{in } C^0([-\tau, 0]; W^{1,q}(\Omega)), \quad \varphi_\varepsilon \to \varphi \quad \text{in } C^1([0, r_0] \times [0, K_n]), \\ f_\varepsilon \to f \quad \text{in } C^1([0, H_0] \times [0, r_0]), \quad K_{c\varepsilon} \to K_c \quad \text{in } C^1([0, H_0]) \end{gathered} \tag{3.13}$$

as $\varepsilon \searrow 0$ for all $r_0 > 0$. Furthermore, we assume that for any $a \in (0, H_0)$ there is $\tilde C_a > 0$ such that

$$f_\varepsilon(h,c) \le \tilde C_a \quad \text{for all } (c,h) \in [0,\infty) \times [a, H_0] \tag{3.14}$$

and all $\varepsilon \in (0,1)$.

3.1 Global existence for the regularized problems

We first state the local existence of classical solutions for (3.11) along with an extensibility criterion and prove this result like in [36, Lemma 3.1].

Lemma 3.3 *Let $\varepsilon \in (0,1)$ and assume that (3.1), (3.2) and (3.12) are fulfilled. Then there exist a maximal existence time $T_\varepsilon \in (0,\infty]$ and functions $c_\varepsilon, n_\varepsilon, h_\varepsilon \in C^{2,1}(\bar\Omega \times [0, T_\varepsilon))$ and $y_\varepsilon \in C^1([0, T_\varepsilon); C^0(\bar\Omega))$ which solve (3.11) in the classical sense and satisfy*

$$\begin{gathered} c_\varepsilon \ge 0, \quad 0 \le n_\varepsilon \le K_n, \quad 0 \le y_\varepsilon \le Y_0 \quad \text{in } \bar\Omega \times [0, T_\varepsilon), \\ 0 \le h_\varepsilon \le H_0 \quad \text{in } \bar\Omega \times [-\tau, T_\varepsilon). \end{gathered} \tag{3.15}$$

If moreover $T_\varepsilon < \infty$ holds, then

$$\limsup_{t \nearrow T_\varepsilon} \Big(\|c_\varepsilon(\cdot,t)\|_{C^0(\bar\Omega)} + \|h_\varepsilon(\cdot,t)\|_{W^{1,q}(\Omega)} \Big) = \infty \tag{3.16}$$

is fulfilled, where $q \in (N+2,\infty)$ is defined in (3.5).

Proof. We fix $\beta \in (0,1)$, $T := 1$ and set

$$A := \|c_{0\varepsilon}\|_{C^{2+\beta}(\bar\Omega)} + \|n_{0\varepsilon}\|_{C^{2+\beta}(\bar\Omega)} + \|h_{0\varepsilon}\|_{C^{2+\beta}(\bar\Omega)} + \|h_{0\varepsilon}\|_{C^{\beta,\frac{\beta}{2}}(\bar\Omega\times[-\tau,0])} + \|y_{0\varepsilon}\|_{C^\beta(\bar\Omega)} < \infty.$$

Moreover, let $c_{0\varepsilon t}(x)$, $n_{0\varepsilon t}(x)$ and $h_{0\varepsilon t}(x)$ denote the right-hand side of the first, second and third equation of (3.11) evaluated at $(x,t) = (x,0)$, respectively, so that

$$\begin{aligned} B \;:=\; & \|c_{0\varepsilon}\|_{C^\beta(\bar\Omega)} + \|c_{0\varepsilon t}\|_{C^0(\bar\Omega)} + \|h_{0\varepsilon}\|_{C^\beta(\bar\Omega)} + \|h_{0\varepsilon t}\|_{C^0(\bar\Omega)} \\ & + \|n_{0\varepsilon}\|_{C^{1+\beta}(\bar\Omega)} + \|n_{0\varepsilon t}\|_{C^1(\bar\Omega)} \qquad \le C_3(A) < \infty \end{aligned} \tag{3.17}$$

holds with some constant $C_3(A)$ depending on A. Then we define

$$\begin{aligned} X \;:=\; & \Big\{ (c_\varepsilon, h_\varepsilon, n_\varepsilon) \in (C^{\beta,\frac{\beta}{2}}(\bar\Omega\times[0,T]))^2 \times C^{1+\beta,\frac{1+\beta}{2}}(\bar\Omega\times[0,T]) \;: \\ & c_\varepsilon \ge 0,\; 0 \le h_\varepsilon \le H_0,\; 0 \le n_\varepsilon \le K_n, \\ & \|c_\varepsilon\|_{C^{\beta,\frac{\beta}{2}}(\bar\Omega\times[0,T])} + \|h_\varepsilon\|_{C^{\beta,\frac{\beta}{2}}(\bar\Omega\times[0,T])} + \|n_\varepsilon\|_{C^{1+\beta,\frac{1+\beta}{2}}(\bar\Omega\times[0,T])} \le B+3 \Big\}. \end{aligned}$$

Given fixed $(c_\varepsilon, h_\varepsilon, n_\varepsilon) \in X$, by (3.1), (3.2), (3.12), the theory of ODEs (see, e.g., [33]) and the comparison principle, there is a solution $y_\varepsilon \in C^1((0,T); C^0(\bar\Omega))$ to the fourth equation of (3.11) with initial data $y_{0\varepsilon}$ such that

$$0 \le y_\varepsilon \le Y_0 \quad \text{in } \bar\Omega\times[0,T], \qquad \|y_\varepsilon\|_{C^{\beta,\frac{\beta}{2}}(\bar\Omega\times[0,T])} + \|\partial_t y_\varepsilon\|_{C^0(\bar\Omega\times[0,T])} \le C_4(A), \tag{3.18}$$

where the latter Hölder estimate with repect to x follows from the regularity properties (3.1) and an application of Gronwall's inequality to $y_\varepsilon(x_1,t) - y_\varepsilon(x_2,t)$. Next, (3.1), (3.2), (3.12), (3.18) along with [21, Theorems V.7.4 and IV.5.3] and the parabolic comparison principle imply the existence of a solution $\tilde h_\varepsilon \in C^{2+\beta,1+\frac{\beta}{2}}(\bar\Omega\times[0,T])$ to the third equation of (3.11) with the homogeneous Neumann boundary condition and initial data $h_{0\varepsilon}$, satisfying

$$\begin{gathered} 0 \le \tilde h_\varepsilon \le H_0 \quad \text{in } \bar\Omega\times[-\tau,T], \\ \|\tilde h_\varepsilon\|_{C^{\beta,\frac{\beta}{2}}(\bar\Omega\times[-\tau,T])} + \|\tilde h_\varepsilon\|_{C^{2+\beta,1+\frac{\beta}{2}}(\bar\Omega\times[0,T])} \le C_5(A) \end{gathered} \tag{3.19}$$

with some constant $C_5(A) > 0$. Using next (3.1), (3.12), (3.18) and (3.19), by the comparison principle, [21, Theorem III.5.1] and [23, Theorem 1.1] there exists a weak solution $\tilde c_\varepsilon \in C^{1+\beta_1,\frac{1+\beta_1}{2}}(\bar\Omega\times[0,T]) \cap W_2^{1,\frac{1}{2}}(\bar\Omega\times[0,T])$ to the first equation of (3.11) (with $\tilde h_\varepsilon$ instead of h_ε) satisfying the respective boundary and initial conditions, where $\beta_1 \in (0,\beta]$. By the last reference and [21, Theorem IV.5.3], we further obtain that $\tilde c_\varepsilon \in C^{2+\beta_1,1+\frac{\beta_1}{2}}(\bar\Omega\times[0,T])$ is a classical solution satisfying

$$\tilde c_\varepsilon \ge 0 \quad \text{in } \bar\Omega\times[0,T], \qquad \|\tilde c_\varepsilon\|_{C^{2+\beta_1,1+\frac{\beta_1}{2}}(\bar\Omega\times[0,T])} \le C_6(A) \tag{3.20}$$

with a positive constant $C_6(A)$. Combining this with (3.12) and (3.19), we apply the theory of ODEs (see e.g. Theorem 2 in [33, Section 2.3]) and the comparison principle to

get a solution $\tilde{n}_\varepsilon \in C^{2+\beta_1,1+\frac{\beta_1}{2}}(\bar{\Omega}\times[0,T])$ to the second equation of (3.11) (with $\tilde{c}_\varepsilon$, $\tilde{h}_\varepsilon$ instead of c_ε, h_ε) with initial data $n_{0\varepsilon}$, such that

$$\begin{aligned} &0 \le \tilde{n}_\varepsilon \le K_n \quad \text{in } \bar{\Omega}\times[0,T], \\ &\|\tilde{n}_\varepsilon\|_{C^{2+\beta_1,1+\frac{\beta_1}{2}}(\bar{\Omega}\times[0,T])} + \|\partial_t \tilde{n}_\varepsilon\|_{C^{1+\beta_1,\frac{1+\beta_1}{2}}(\bar{\Omega}\times[0,T])} \le C_7(A), \end{aligned} \tag{3.21}$$

with some positive constant $C_7(A)$, where the Hölder estimate with respect to x is done as described above for y_ε. In particular, recalling the definitions of $c_{0\varepsilon t}$, $h_{0\varepsilon t}$ and $n_{0\varepsilon t}$ before (3.17), from (3.19)-(3.21) we obtain $c_{0\varepsilon t}(x) = \partial_t \tilde{c}_\varepsilon(x,0)$, $h_{0\varepsilon t}(x) = \partial_t \tilde{h}_\varepsilon(x,0)$ and $n_{0\varepsilon t}(x) = \partial_t \tilde{n}_\varepsilon(x,0)$ for $x \in \bar{\Omega}$ so that there is $T_0 \in (0,T]$ only depending on A such that

$$\|\tilde{c}_\varepsilon\|_{C^{\beta,\frac{\beta}{2}}(\bar{\Omega}\times[0,T])} + \|\tilde{h}_\varepsilon\|_{C^{\beta,\frac{\beta}{2}}(\bar{\Omega}\times[0,T])} + \|n_\varepsilon\|_{C^{1+\beta,\frac{1+\beta}{2}}(\bar{\Omega}\times[0,T])} \le B+3. \tag{3.22}$$

Here we used that $\|\psi\|_{C^{\frac{\beta}{2}}([0,T_0])} \le \|\psi\|_{C^1([0,T_0])}$ holds for $\psi \in C^1([0,T_0])$ due to $T_0 \le 1$. Hence, setting $T := T_0$, the map $F : X \to X$, $F(c_\varepsilon, h_\varepsilon, n_\varepsilon) := (\tilde{c}_\varepsilon, \tilde{h}_\varepsilon, \tilde{n}_\varepsilon)$ is well-defined and compact due to (3.19)-(3.22) so that F has a fixed point $(c_\varepsilon, h_\varepsilon, n_\varepsilon)$ by Schauder's fixed point theorem. The above reasoning thus ensures the existence of a classical solution to (3.11) in $\Omega\times(0,T)$ which has the claimed regularity properties and satisfies (3.15).
Next, let $T_\varepsilon < \infty$ and assume for contradiction that (3.16) does not hold. Then there is $C_8 > 0$ such that

$$\|c_\varepsilon\|_{L^\infty(\Omega\times(0,T_\varepsilon))} + \|h_\varepsilon\|_{L^\infty((0,T_\varepsilon);W^{1,q}(\Omega))} \le C_8. \tag{3.23}$$

Combining this estimate with (3.1), (3.12), (3.15) and (3.11), we have

$$\partial_t c_\varepsilon = \nabla\cdot(a_\varepsilon(x,t,\nabla c_\varepsilon)) + b_\varepsilon(x,t) \qquad \text{in } \Omega\times(0,T_\varepsilon),$$

where

$$a_\varepsilon(x,t,\xi)\cdot\xi \ge \frac{\tilde{C}_2}{2(1+C_8)}|\xi|^2 - \psi_0(x,t), \quad |a_\varepsilon(x,t,\xi)| \le \tilde{C}_1|\xi| + \psi_1(x,t)$$

holds for all $(x,t,\xi) \in \Omega\times(0,T_\varepsilon)\times\mathbb{R}^N$ with $\psi_0, \psi_1^2 \in L^\infty((0,T_\varepsilon); L^{\frac{q}{2}}(\Omega))$ and $b_\varepsilon \in L^\infty(\Omega\times(0,T_\varepsilon))$. Hence, in view of $\frac{q}{2} > \frac{N}{2}$, [34, Theorem 1.3 and Remark 1.4] and (3.1) imply that

$$\|c_\varepsilon\|_{C^{\beta_2,\frac{\beta_2}{2}}(\bar{\Omega}\times[0,T_\varepsilon])} \le C_9 \tag{3.24}$$

with some $C_9 > 0$ and $\beta_2 \in (0,1)$. By using the same results and possibly diminishing β_2, we also have

$$\|h_\varepsilon\|_{C^{\beta_2,\frac{\beta_2}{2}}(\bar{\Omega}\times[0,T_\varepsilon])} \le C_{10},$$

where $C_{10} > 0$ and $\beta_2 \in (0,1)$. Hence, (3.18) and (3.19) are valid with $T = T_\varepsilon$ and $\beta = \beta_2$ so that a combination with (3.24) yields

$$\|n_\varepsilon\|_{C^{\beta_2,\frac{\beta_2}{2}}(\bar{\Omega}\times[0,T_\varepsilon])} \le C_{11}$$

with some $C_{11} > 0$. Thus, we are able to apply [23, Theorem 1.1] to obtain

$$\|c_\varepsilon\|_{C^{1+\beta_3,\frac{1+\beta_3}{2}}(\bar{\Omega}\times[0,T_\varepsilon])} \le C_{12}$$

with constants $C_{12} > 0$ and $\beta_3 \in (0, \beta_2]$. Now this implies

$$\|n_\varepsilon\|_{C^{1+\beta_3, \frac{1+\beta_3}{2}}(\bar{\Omega}\times[0,T_\varepsilon])} \le C_{13}$$

with some $C_{13} > 0$ due to (3.19) and [33, Theorem 2 in Section 2.3]. Finally, as A with $\beta = \beta_3$ is finite, (3.18)-(3.21) yield

$$\begin{aligned} A_1 \;:=\; & \|c_\varepsilon\|_{C^{2+\beta_4, 1+\frac{\beta_4}{2}}(\bar{\Omega}\times[0,T_\varepsilon])} + \|n_\varepsilon\|_{C^{2+\beta_4, 1+\frac{\beta_4}{2}}(\bar{\Omega}\times[0,T_\varepsilon])} + \|h_\varepsilon\|_{C^{2+\beta_4, 1+\frac{\beta_4}{2}}(\bar{\Omega}\times[0,T_\varepsilon])} \\ & + \|h_\varepsilon\|_{C^{\beta_4, \frac{\beta_4}{2}}(\bar{\Omega}\times[-\tau,T_\varepsilon])} + \|y_{0\varepsilon}\|_{C^{\beta_4, \frac{\beta_4}{2}}(\bar{\Omega}\times[0,T_\varepsilon])} < \infty \end{aligned}$$

with some $\beta_4 \in (0, \beta_3]$. Therefore, by the first part of this proof the solution can be extended to a classical solution of (3.11) in $\Omega \times (0, T_\varepsilon + \frac{T_0}{2})$ with some $T_0 = T_0(A_1) > 0$ which contradicts the maximality of T_ε and proves (3.16). □

In order to prove the global existence for the solution to (3.11), we will show appropriate bounds on c_ε and ∇h_ε which are independent of ε. To this end, we remark that (3.1), (3.12) and (3.13) imply

$$\begin{gathered} 0 < a_2 \le K_c(h) \le a_1, \quad 0 < b_2 \le \mu_c(y) \le b_1, \quad |R(y,h)| \le M_R \\ \text{for all } h \in [0, H_0],\ y \in [0, Y_0] \end{gathered} \tag{3.25}$$

with positive constants b_1, b_2, M_R. Moreover, we denote by $(e^{t\Delta})_{t\ge 0}$ the heat semigroup in Ω with homogeneous Neumann boundary conditions and define $\lambda_1 > 0$ to be the first nonzero eigenvalue of $-\Delta$ in Ω under Neumann boundary conditions. It is well-known (see e.g. [45, Lemma 1.3]) that there exists $C_3 > 0$ such that

$$\begin{aligned} &\|\nabla e^{t\Delta} v\|_{L^\rho(\Omega)} \le C_3 \left(1 + t^{-\frac{1}{2} - \frac{N}{2}(\frac{1}{r} - \frac{1}{\rho})}\right) e^{-\lambda_1 t} \|v\|_{L^r(\Omega)} && \text{for all } t > 0 \\ &\|\nabla e^{t\Delta} w\|_{L^p(\Omega)} \le C_3 e^{-\lambda_1 t} \|\nabla w\|_{L^p(\Omega)} && \text{for all } t > 0 \end{aligned} \tag{3.26}$$

holds for any $v \in L^r(\Omega)$, $w \in W^{1,p}(\Omega)$, $1 \le r \le \rho \le \infty$ and $p \in [2, \infty)$. Using these estimates, we prove the following elementary bounds for c_ε and h_ε.

Lemma 3.4 *Let $q \in (N+2, \infty)$ be as defined in (3.5). There exists $C > 0$ such that for all $\varepsilon \in (0,1)$ we have*

$$\int_\Omega c_\varepsilon(x,t)\,dx \le m := \max\left\{ \sup_{\varepsilon\in(0,1)} \int_\Omega c_{0\varepsilon}\,dx, \frac{a_1 b_1 |\Omega|}{b_2} \right\} < \infty \qquad \textit{for all } t \in (0, T_\varepsilon), \tag{3.27}$$

$$\|h_\varepsilon(\cdot,t)\|_{W^{1,q}(\Omega)} \le C \qquad \textit{for all } t \in (0, T_\varepsilon). \tag{3.28}$$

Proof. Integrating the first equation of (3.11) and using (3.15), (3.25) along with the Cauchy-Schwarz inequality, we have

$$\frac{d}{dt}\int_\Omega c_\varepsilon \le b_1 \int_\Omega c_\varepsilon - \frac{b_2}{a_1}\int_\Omega c_\varepsilon^2 \le b_1 \int_\Omega c_\varepsilon - \frac{b_2}{a_1|\Omega|}\left(\int_\Omega c_\varepsilon\right)^2 \quad \text{for all } t \in (0, T_\varepsilon),$$

so that (3.27) follows by an ODE comparison and (3.13).
Next, we use the Neumann heat semigroup and Lemma 3.3 to obtain from (3.11)

$$h_\varepsilon(\cdot,t) = e^{tD_h\Delta} h_{0\varepsilon}(\cdot,0) + \int_0^t e^{(t-s)D_h\Delta} R(y_\varepsilon(\cdot,s), h_\varepsilon(\cdot,s))\,ds, \quad t \in (0, T_\varepsilon).$$

In view of $q \geq 2$, (3.15), (3.25) and (3.26), this implies

$$\begin{aligned}
&\|\nabla h_\varepsilon(\cdot,t)\|_{L^q(\Omega)} \\
&\quad \leq \|\nabla e^{tD_h\Delta} h_{0\varepsilon}(\cdot,0)\|_{L^q(\Omega)} + \int_0^t \|\nabla e^{(t-s)D_h\Delta} R(y_\varepsilon(\cdot,s),h_\varepsilon(\cdot,s))\|_{L^q(\Omega)}\,ds \\
&\quad \leq C_3 \|h_{0\varepsilon}(\cdot,0)\|_{W^{1,q}(\Omega)} \\
&\qquad + C_3 \int_0^t \left(1+(D_h(t-s))^{-\frac{1}{2}}\right) e^{-\lambda_1 D_h(t-s)} \|R(y_\varepsilon(\cdot,s),h_\varepsilon(\cdot,s))\|_{L^q(\Omega)}\,ds \\
&\quad \leq C_3 \sup_{\varepsilon\in(0,1)} \|h_{0\varepsilon}(\cdot,0)\|_{W^{1,q}(\Omega)} + C_3 M_R |\Omega|^{\frac{1}{q}} \int_0^\infty \left(1+(D_h\sigma)^{-\frac{1}{2}}\right) e^{-\lambda_1 D_h \sigma}\,d\sigma
\end{aligned}$$

for all $t \in (0,T_\varepsilon)$, which proves (3.28) due to (3.13) and (3.15). □

The next lemma is the main step towards the global existence. It uses Lemma 3.4 as a starting point to obtain bounds in $L^\infty((0,T);L^p(\Omega))$ for any finite p. We adapt ideas from [40, Lemma 3.3] for its proof.

Lemma 3.5 *Let $T \in (0,\infty)$ such that $T \leq T_\varepsilon$. Then there are $C(T) > 0$ and $\tilde{C}(T) > 0$ such that*

$$h_\varepsilon(x,t) \geq C(T) \quad \text{for all } (x,t) \in \bar{\Omega} \times [0,T), \tag{3.29}$$

$$\int_0^T \int_\Omega |\nabla c_\varepsilon|^2(x,t)\,dxdt \leq \tilde{C}(T) \tag{3.30}$$

are fulfilled for every $\varepsilon \in (0,1)$. Moreover, for any $p \in [1,\infty)$ there exists $C_p(T) > 0$ such that for all $\varepsilon \in (0,1)$ we have

$$\|c_\varepsilon(\cdot,t)\|_{L^p(\Omega)} \leq C_p(T) \qquad \text{for all } t \in (0,T). \tag{3.31}$$

Proof. In view of (3.1), (3.2) and (3.15), there exists $C_R > 0$ such that the third equation in (3.11) implies

$$\partial_t h_\varepsilon \geq D_h \Delta h_\varepsilon + R(y_\varepsilon,0) - C_R h_\varepsilon \geq D_h \Delta h_\varepsilon - C_R h_\varepsilon \quad \text{in } \Omega \times (0,T_\varepsilon)$$

for all $\varepsilon \in (0,1)$. Hence, by (3.12) and the comparison principle, we have

$$h_\varepsilon(x,t) \geq \frac{\delta}{2} e^{-C_R t} \qquad \text{for all } (x,t) \in \bar{\Omega} \times [0,T_\varepsilon) \tag{3.32}$$

and all $\varepsilon \in (0,1)$, which proves (3.29).
Next, we fix $p \in [2,\infty)$ and $T \in (0,\infty)$ such that $T \leq T_\varepsilon$. Defining $a := C(T) > 0$ with $C(T)$ from (3.29), testing the first equation in (3.11) by $(1+c_\varepsilon)^{p-1}$ and using (3.12), (3.14), (3.15), (3.25) as well as the inequalities of Young and Hölder, we obtain

$$\begin{aligned}
\frac{1}{p}\frac{d}{dt}\int_\Omega (1+c_\varepsilon)^p &= \int_\Omega (1+c_\varepsilon)^{p-1}\partial_t c_\varepsilon \\
&\leq -(p-1)\int_\Omega \varphi_\varepsilon(c_\varepsilon,n_\varepsilon)(1+c_\varepsilon)^{p-2}|\nabla c_\varepsilon|^2 \\
&\quad +(p-1)\int_\Omega f_\varepsilon(h_\varepsilon,c_\varepsilon)(1+c_\varepsilon)^{p-2}\nabla c_\varepsilon \cdot \nabla h_\varepsilon \\
&\quad +b_1 \int_\Omega c_\varepsilon(1+c_\varepsilon)^{p-1} - \frac{b_2}{a_1}\int_\Omega c_\varepsilon^2(1+c_\varepsilon)^{p-1}
\end{aligned}$$

$$
\begin{aligned}
&\leq -\frac{\tilde{C}_2(p-1)}{2}\int_\Omega (1+c_\varepsilon)^{p-3}|\nabla c_\varepsilon|^2 + \frac{\tilde{C}_a^2(p-1)}{2\tilde{C}_2}\int_\Omega (1+c_\varepsilon)^{p-1}|\nabla h_\varepsilon|^2 \\
&\quad + \left(b_1 + \frac{2b_2}{a_1}\right)\int_\Omega (1+c_\varepsilon)^p - \frac{b_2}{a_1}\int_\Omega (1+c_\varepsilon)^{p+1} \\
&\leq -\frac{2\tilde{C}_2}{p-1}\int_\Omega |\nabla (1+c_\varepsilon)^{\frac{p-1}{2}}|^2 \\
&\quad + \frac{\tilde{C}_a^2(p-1)}{2\tilde{C}_2}\left(\int_\Omega (1+c_\varepsilon)^{\frac{(p-1)q}{q-2}}\right)^{\frac{q-2}{q}}\left(\int_\Omega |\nabla h_\varepsilon|^q\right)^{\frac{2}{q}} \\
&\quad + \left(b_1 + \frac{2b_2}{a_1}\right)\int_\Omega (1+c_\varepsilon)^p - \frac{b_2}{a_1|\Omega|^{\frac{1}{p}}}\left(\int_\Omega (1+c_\varepsilon)^p\right)^{\frac{p+1}{p}} \qquad (3.33)
\end{aligned}
$$

for all $t \in (0,T)$ in view of $q > 2$. Abbreviating $\theta := \frac{q}{q-2} \in (1, \frac{N+2}{N})$, the Gagliardo-Nirenberg inequality and (3.27) yield

$$
\begin{aligned}
\left(\int_\Omega (1+c_\varepsilon)^{(p-1)\theta}\right)^{\frac{1}{\theta}} &= \left\|(1+c_\varepsilon)^{\frac{p-1}{2}}\right\|^2_{L^{2\theta}(\Omega)} \\
&\leq C_{GN}\left\|\nabla(1+c_\varepsilon)^{\frac{p-1}{2}}\right\|^{2d}_{L^2(\Omega)}\left\|(1+c_\varepsilon)^{\frac{p-1}{2}}\right\|^{2(1-d)}_{L^{\frac{2}{p-1}}(\Omega)} \\
&\quad + C_{GN}\left\|(1+c_\varepsilon)^{\frac{p-1}{2}}\right\|^2_{L^{\frac{2}{p-1}}(\Omega)} \\
&\leq C_{GN}\Big((m+|\Omega|)^{(p-1)(1-d)}\left\|\nabla(1+c_\varepsilon)^{\frac{p-1}{2}}\right\|^{2d}_{L^2(\Omega)} \\
&\quad + (m+|\Omega|)^{p-1}\Big) \qquad (3.34)
\end{aligned}
$$

for all $t \in (0, T_\varepsilon)$, since

$$
d := \frac{\frac{p-1}{2} - \frac{1}{2\theta}}{\frac{1}{N} - \frac{1}{2} + \frac{p-1}{2}} \in (0,1)
$$

is satisfied due to $\theta \in (1, \frac{N+2}{N})$ and $p \geq 2$. In view of (3.28) and $d < 1$, by inserting (3.34) into (3.33) and applying Young's inequality we arrive at

$$
\begin{aligned}
&\frac{1}{p}\frac{d}{dt}\int_\Omega (1+c_\varepsilon)^p + \frac{\tilde{C}_2}{p-1}\int_\Omega |\nabla(1+c_\varepsilon)^{\frac{p-1}{2}}|^2 \\
&\leq \left(b_1 + \frac{2b_2}{a_1}\right)\int_\Omega (1+c_\varepsilon)^p - \frac{b_2}{a_1|\Omega|^{\frac{1}{p}}}\left(\int_\Omega (1+c_\varepsilon)^p\right)^{\frac{p+1}{p}} + C_4(a,p) \qquad (3.35)
\end{aligned}
$$

for all $t \in (0,T)$ and $\varepsilon \in (0,1)$ with some positive constant $C_4(a,p)$. This proves (3.31) upon an ODE comparison due to (3.13) and (3.27). Then, integrating (3.35) for $p = 3$ with respect to $t \in (0,T)$ and using (3.31), we conclude that (3.30) is valid. □

Now we are in the position to obtain the global existence for the regularized problem (3.11) by using a result from [40].

Lemma 3.6 *For any $\varepsilon \in (0,1)$, the solution to (3.11) obtained in Lemma 3.3 exists globally in time, which means that $T_\varepsilon = \infty$. Furthermore, for any $T \in (0,\infty)$ there exists $C_\infty(T) > 0$ such that*

$$
0 \leq c_\varepsilon \leq C_\infty(T) \quad \text{in } \bar{\Omega} \times [0,T] \qquad (3.36)
$$

holds for any $\varepsilon \in (0,1)$.

Proof. We fix $T \in (0,\infty)$ with $T \le T_\varepsilon$. Keeping the notation from [40, Appendix A], by (3.11), (3.12), (3.14) and Lemmas 3.3-3.5, we have

$$\partial_t c_\varepsilon \le \nabla \cdot (D_\varepsilon(x,t,c_\varepsilon)\nabla c_\varepsilon) + \nabla \cdot (F_\varepsilon(x,t)) + G_\varepsilon(x,t), \quad (x,t) \in \Omega \times (0,T),$$

where c_ε and F_ε satisfy the homogeneous Neumann boundary condition, D_ε and F_ε are C^1-functions and G_ε is continuous such that $F_\varepsilon \in L^\infty((0,T);L^{q_1}(\Omega))$, $G_\varepsilon \in L^\infty((0,T);L^{q_2}(\Omega))$, $c_\varepsilon \in L^\infty((0,T);L^{p_0}(\Omega))$ and $D_\varepsilon(x,t,c_\varepsilon) \ge \tilde{C}_2(1+c_\varepsilon)^{\tilde{m}-1}$ for $\tilde{m}=0$, $q_1 = q > N+2$ and all $p_0 \in (1,\infty)$ and $q_2 \in (\frac{N+2}{2},\infty]$. In view of $\tilde{m}=0$, we may apply [40, Lemma A.1] with some $p_0 > \max\{1, \frac{N}{2}\}$ and obtain a constant $C_\infty(T) > 0$ such that

$$\|c_\varepsilon\|_{L^\infty(\Omega\times(0,T))} \le C_\infty(T).$$

As $C_\infty(T)$ depends on $\tilde{C}_2$, $\sup_{\varepsilon\in(0,1)} \|c_{0\varepsilon}\|_{L^\infty(\Omega)}$ and the norms of c_ε, F_ε and G_ε in the spaces mentioned above, we conclude that $C_\infty(T)$ does not depend on $\varepsilon \in (0,1)$ and just depends on T via (3.29) and (3.31). Hence, in view of (3.28), the criterion (3.16) proves the lemma. □

Let us finalize this subsection with the following remark.

Remark 3.7 *The conditions imposed on φ and f in* (3.3) *and* (3.4) *are motivated by biological considerations and are in particular satisfied for the example given in* (2.6).
If we assume instead

$$0 \le f(h,c) \le C_1, \quad \frac{C_2}{1+c} \le \varphi(c,n) \le C_1 \quad \forall (c,n,h) \in [0,\infty)\times[0,K_n]\times[0,H_0]$$

and corresponding estimates for φ_ε and f_ε, then $\|c_\varepsilon\|_{L^\infty(\Omega\times(0,\infty))} \le C_\infty$ holds for some $C_\infty > 0$ which does not depend on $\varepsilon \in (0,1)$, as the constants C_p and C_∞ do not depend on T any more. This result remains true if we only assume the nonnegativity of h_0 and $h_{0\varepsilon}$ instead of their strict positivity as we do not need (3.29) *in this setting.*
With appropriately adapted proofs of Lemmas 3.5 and 3.6, the result $\|c_\varepsilon\|_{L^\infty(\Omega\times(0,\infty))} \le C_\infty$ holds for some $C_\infty > 0$ which does not depend on $\varepsilon \in (0,1)$, if we assume

$$0 \le f(h,c) \le C_1(1+c)^{m_1}, \quad C_2(1+c)^{-m_2} \le \varphi(c,n) \le C_1(1+c)^{m_3}$$

for all $(c,n,h) \in [0,\infty)\times[0,K_n]\times[0,H_0]$ with some real numbers m_j, $j=1,2,3$, satisfying $2m_1 + m_2 < 3$ as well as $h_0 \in C^0([-\tau,0];W^{1,\infty}(\Omega))$ and the nonnegativity of h_0.

3.2 Existence of a global weak solution to the original problem

In order to obtain a global weak solution to (2.3), we next prove appropriate precompactness properties of the solutions to (3.11) which are based on the results of the preceding subsection.

Lemma 3.8 *Let $T \in (0,\infty)$ be arbitrary. For the global solutions to* (3.11) *from Lemma 3.3 we have that $(c_\varepsilon)_{\varepsilon\in(0,1)}$, $(n_\varepsilon)_{\varepsilon\in(0,1)}$, $(h_\varepsilon)_{\varepsilon\in(0,1)}$ and $(y_\varepsilon)_{\varepsilon\in(0,1)}$ are strongly precompact in $L^2(\Omega\times(0,T))$.*

Proof. Throughout this proof we will frequently make use of (3.12), (3.15), (3.25), (3.28), (3.30) and (3.36) without explicitly mentioning this every time. Using these properties, there exists a constant $C_4(T) > 0$ such that for all $\psi \in C_0^\infty(\Omega)$ and all $\varepsilon \in (0,1)$ we obtain from (3.11) and the Hölder inequality that

$$\int_\Omega \partial_t c_\varepsilon \psi \;=\; -\int_\Omega \varphi_\varepsilon(c_\varepsilon,n_\varepsilon)\nabla c_\varepsilon \cdot \nabla\psi + \int_\Omega f_\varepsilon(h_\varepsilon,c_\varepsilon)\nabla h_\varepsilon \cdot \nabla\psi$$

$$
\begin{aligned}
&+\int_\Omega \mu_c(y_\varepsilon)c_\varepsilon\left(1-\frac{c_\varepsilon}{K_c(h_\varepsilon(\cdot,t-\tau))}-\eta_1\frac{n_\varepsilon}{K_n}\right)\psi\\
\le\ &\left[C_4(T)+\left(\int_\Omega|\nabla c_\varepsilon|^2\right)^{\frac12}\right]\|\psi\|_{W_0^{1,2}(\Omega)} \qquad \text{for all } t\in(0,T).
\end{aligned}
$$

Hence, $(\partial_t c_\varepsilon)_{\varepsilon\in(0,1)}$ is uniformly bounded in $L^2((0,T);(W_0^{1,2})^*)$ by (3.30). As furthermore $(c_\varepsilon)_{\varepsilon\in(0,1)}$ is uniformly bounded in $L^2((0,T);W^{1,2}(\Omega))$, $W^{1,2}(\Omega)$ is compactly embedded into $L^2(\Omega)$ and $L^2(\Omega)\subset(W_0^{1,2})^*$, the Aubin-Lions lemma (see [41, Theorem 2.1 in Chapter III]) implies the strong precompactness of $(c_\varepsilon)_{\varepsilon\in(0,1)}$ in $L^2((0,T);L^2(\Omega))$.
Similarly, $(\partial_t h_\varepsilon)_{\varepsilon\in(0,1)}$ and $(h_\varepsilon)_{\varepsilon\in(0,1)}$ are uniformly bounded in $L^2((0,T);(W_0^{1,2})^*)$ and $L^2((0,T);W^{1,2}(\Omega))$, respectively, in view of $q\ge 2$, so that $(h_\varepsilon)_{\varepsilon\in(0,1)}$ is strongly precompact in $L^2((0,T);L^2(\Omega))$.
In order to prove the claimed results for $(n_\varepsilon)_{\varepsilon\in(0,1)}$, we recall that by Kolmogorov-Riesz for a bounded domain $\mathcal{D}\subset\mathbb{R}^s$ with $s\in\mathbb{N}$ a set $\mathcal{M}\subset L^2(\mathcal{D})$ is strongly precompact in $L^2(\mathcal{D})$ if and only if

$$
\sup_{F\in\mathcal{M}}\|F\|_{L^2(\mathcal{D})}<\infty \quad\text{and}\quad \lim_{z\to 0}\left(\sup_{F\in\mathcal{M}}\|F^z-F\|_{L^2(\mathcal{D})}\right)=0,
$$

where $z\in\mathbb{R}^s$ and $F^z(\zeta):=F(\zeta+z)$ for $\zeta\in\mathcal{D}$ such that $\zeta+z\in\mathcal{D}$ and $F^z(\zeta)=0$ if $\zeta+z\notin\mathcal{D}$. Setting $\mathcal{D}:=\Omega\times(0,T)$ and $\zeta:=(x,t)\in\mathcal{D}$, for $z\in\mathbb{R}^{N+1}$ we obtain from an integration of the second equation of (3.11) and the regularity and boundedness properties of its right-hand side that

$$
\begin{aligned}
&\int_\Omega (n_\varepsilon^z-n_\varepsilon)^2(\cdot,t)\,dx\\
&\le \int_\Omega (n_{0\varepsilon}^z-n_{0\varepsilon})^2\,dx + C_5(T)\int_0^t\int_\Omega\left(|n_\varepsilon^z-n_\varepsilon|+|c_\varepsilon^z-c_\varepsilon|+|h_\varepsilon^z-h_\varepsilon|\right)|n_\varepsilon^z-n_\varepsilon|\,dxds\\
&\le \int_\Omega (n_{0\varepsilon}^z-n_{0\varepsilon})^2\,dx + C_6(T)\int_0^t\int_\Omega\left((n_\varepsilon^z-n_\varepsilon)^2+(c_\varepsilon^z-c_\varepsilon)^2+(h_\varepsilon^z-h_\varepsilon)^2\right)dxds \qquad (3.37)
\end{aligned}
$$

with some positive constants $C_5(T)$ and $C_6(T)$ for all $t\in(0,T)$ and all $\varepsilon\in(0,1)$. Hence, by Gronwall's inequality there exists $C_7(T)>0$ such that

$$
\begin{aligned}
&\sup_{\varepsilon\in(0,1)}\|n_\varepsilon^z-n_\varepsilon\|_{L^2(\Omega\times(0,T))}\\
&\le C_7(T)\sup_{\varepsilon\in(0,1)}\left(\|n_{0\varepsilon}^z-n_{0\varepsilon}\|_{L^2(\Omega)}+\|c_\varepsilon^z-c_\varepsilon\|_{L^2(\Omega\times(0,T))}+\|h_\varepsilon^z-h_\varepsilon\|_{L^2(\Omega\times(0,T))}\right). \qquad (3.38)
\end{aligned}
$$

As $(c_\varepsilon)_{\varepsilon\in(0,1)}$, $(h_\varepsilon)_{\varepsilon\in(0,1)}$ are strongly precompact in $L^2(\Omega\times(0,T))$ and $(n_{0_\varepsilon})_{\varepsilon\in(0,1)}$ is strongly precompact in $L^2(\Omega)$ due to (3.13), the right-hand side of (3.38) converges to zero as $z\to 0$ by Kolmogorov-Riesz. Since furthermore $(n_\varepsilon)_{\varepsilon\in(0,1)}$ is uniformly bounded in $L^2(\Omega\times(0,T))$, the mentioned criterion yields the strong precompactness of $(n_\varepsilon)_{\varepsilon\in(0,1)}$ in $L^2(\Omega\times(0,T))$.
Similar arguments also show that $(y_\varepsilon)_{\varepsilon\in(0,1)}$ is strongly precompact in $L^2(\Omega\times(0,T))$. □

With these compactness properties at hand, we are able to prove the existence of a global weak solution to the original problem (2.3).

Proof of Theorem 3.2. By Lemma 3.8, (3.13), (3.15), (3.28), (3.30), (3.36) as well

as a standard extraction argument involving diagonal sequences, there are a sequence $(\varepsilon_j)_{j\in\mathbb{N}} \subset (0,1)$ such that $\varepsilon_j \searrow 0$ as $j \to \infty$ and functions

$$c \in L^\infty_{loc}(\bar\Omega \times [0,\infty)) \cap L^2_{loc}([0,\infty); W^{1,2}(\Omega)), \quad n, y \in L^\infty(\Omega \times (0,\infty)),$$
$$h \in L^\infty(\Omega \times (-\tau,\infty)) \cap L^\infty((0,\infty); W^{1,q}(\Omega))$$

satisfying (3.10) such that

$$c_\varepsilon \to c, \quad n_\varepsilon \to n, \quad y_\varepsilon \to y \quad \text{strongly in } L^2_{loc}([0,\infty); L^2(\Omega)) \text{ and a.e. in } \Omega \times (0,\infty),$$
$$h_\varepsilon \to h \quad \text{strongly in } L^2_{loc}([-\tau,\infty); L^2(\Omega)) \text{ and a.e. in } \Omega \times (-\tau,\infty),$$
$$\nabla c_\varepsilon \rightharpoonup \nabla c, \quad \nabla h_\varepsilon \rightharpoonup \nabla h \quad \text{weakly in } L^2_{loc}([0,\infty); L^2(\Omega))$$

as $\varepsilon = \varepsilon_j \searrow 0$. Combining these properties with (3.1), (3.12) and (3.13), for any fixed $T \in (0,\infty)$ we may then pass to the limit as $\varepsilon_j \searrow 0$ in the weak formulation of (3.11) corresponding to (3.6)-(3.9) and use the dominated convergence theorem to conclude that (c, n, h, y) is a global weak solution to (2.3)-(2.5).
In order to prove the uniqueness claim, let in addition $c_0 \in C^\beta(\bar\Omega)$ be fulfilled with some $\beta \in (\frac{1}{N+2}, 1)$ and assume that (c_j, n_j, h_j, y_j), $j = 1, 2$, are global weak solutions to (2.3)-(2.5) such that for all $T \in (0,\infty)$ there is $C_4(T) > 0$ with

$$\begin{aligned} &\|c_j\|_{L^\infty(\Omega\times(0,T))} + \|\nabla c_j\|_{L^2(\Omega\times(0,T))} + \|n_j\|_{L^\infty(\Omega\times(0,T))} \\ &+\|h_j\|_{L^\infty(\Omega\times(0,T))} + \|\nabla h_j\|_{L^r(\Omega\times(0,T))} + \|y_j\|_{L^\infty(\Omega\times(0,T))} \quad \le \quad C_4(T) \end{aligned} \tag{3.39}$$

for $j = 1, 2$ and some $r > N + 2$ which is independent of $T \in (0,\infty)$ and satisfies $1 - \frac{N+1}{r} < \beta$. Observe that the global weak solution constructed above satisfies (3.39) in view of $q > N + 2$.
We next fix an arbitrary $T \in (0,\infty)$. Then, similarly to (3.37) and (3.38), we obtain from (3.7), (3.9), (3.1), (3.39) and Gronwall's inequality that there is $C_5(T) > 0$ such that

$$|n_1 - n_2|(x,t) \quad \le \quad C_5(T) \int_0^t (|c_1 - c_2| + |h_1 - h_2|)(x,s)\, ds \tag{3.40}$$

$$|y_1 - y_2|(x,t) \quad \le \quad C_5(T) \int_0^t (|c_1 - c_2| + |h_1 - h_2|)(x,s)\, ds \tag{3.41}$$

are fulfilled for a.e. $(x,t) \in \Omega \times (0,T)$. Furthermore, (3.8), (3.1) and (3.39) imply

$$\begin{aligned} \int_\Omega |h_1 - h_2|^2(x,t)\, dx \quad \le \quad & -D_h \int_0^t \int_\Omega |\nabla(h_1 - h_2)|^2\, dxds \\ & +C_6(T) \int_0^t (|h_1 - h_2|^2 + |c_1 - c_2|^2 + |n_1 - n_2|^2)\, dxds \end{aligned}$$

for a.e. $t \in (0,T)$ with some $C_6(T) > 0$. Hence, using (3.40) along with Gronwall's inequality we conclude that there is $C_7(T) > 0$ such that

$$\int_\Omega |h_1 - h_2|^2(x,t)\, dx \quad \le \quad C_7(T) \int_0^t |c_1 - c_2|^2(x,s)\, dxds, \tag{3.42}$$

$$\int_0^t \int_\Omega |\nabla(h_1 - h_2)|^2\, dxds \quad \le \quad C_7(T) \int_0^t |c_1 - c_2|^2(x,s)\, dxds \tag{3.43}$$

for a.e. $t \in (0,T)$. Next, in view of (3.1), (3.39) and $c_0 \in C^\beta(\bar\Omega)$, we may apply [34, Theorem 1.3 and Remark 1.4] to obtain that $c_j, h_j \in C^{\gamma,\frac{\gamma}{2}}(\bar\Omega \times [0,T])$ for some $\gamma \in (0,\beta)$

(like in the proof of (3.24)) which also implies $n_j, y_j \in C^0(\bar{\Omega}\times[0,T])$, $j=1,2$, due to (3.40), (3.41). Therefore, the closed operator $\mathcal{B}_j(t)$ with $\mathcal{B}_j(t)u := -\nabla\cdot(\varphi(c_j(\cdot,t),n_j(\cdot,t))\nabla u)$ for $u \in W^{1,r}(\Omega)$, defines a continuous map $\mathcal{B}_j : [0,T] \to \mathcal{L}(W^{1,r}(\Omega), W^{-1,r}(\Omega))$ by [15, (6.3)]. As furthermore $-\mathcal{B}_j$ is uniformly elliptic on $[0,T]$, c_j solves

$$\partial_t u(t) + \mathcal{B}_j(t)u(t) = f_j(t), \quad t \in [0,T], \qquad u(0) = c_0$$

with $f_j \in L^r((0,T);W^{-1,r}(\Omega))$ and $c_0 \in W^{1-\frac{1}{r},r}(\Omega)$ due to (3.1), (3.6), (3.39), $\beta > 1-\frac{N+1}{r}$ and the smoothness of $\partial\Omega$, we may apply the result of maximal parabolic regularity from [15, Theorem 5.4, Remark 5.5, Proposition 6.1] to conclude that $c_j \in W^{1,r}((0,T);W^{-1,r}(\Omega)) \cap L^r((0,T);W^{1,r}(\Omega))$. Here, the regularity of c_0 and [15, Theorem 6.14] shows that we can apply the maximal regularity result also to $u(0) = c_0 \not\equiv 0$. Hence,

$$\|\nabla c_j\|_{L^r(\Omega\times(0,T))} \le C_8(T) \tag{3.44}$$

is satisfied for $j=1,2$ with some $C_8(T) > 0$. Finally, using (3.39)-(3.44), we can apply the method from the uniqueness proof in [30, Theorem 3.1] (starting at [30, (3.37)] and setting $\psi \equiv 0$, $l := h$ and $2p := r > N+2$) to conclude that there is $t_0 \in (0,T)$ sufficiently small (just depending on T) such that

$$\|c_1 - c_2\|^2_{L^\infty((0,t);L^2(\Omega))} \le C_9(T)\int_0^t \|c_1 - c_2\|^2_{L^\infty((0,s);L^2(\Omega))}\,ds$$

holds for all $t \in (0,t_0)$ with some $C_9(T) > 0$. Hence, an application of Gronwall's inequality yields $c_1 = c_2$ a.e. in $\Omega\times(0,t_0)$ so that (3.40)-(3.42) and an iteration of this argument show that the two global weak solutions coincide a.e. in $\Omega\times(0,T)$. □

4 Numerical simulations

For the numerical simulations we first introduce the dimensionless variables

$$\tilde{c} = \frac{c}{C_0}, \quad \tilde{n} = \frac{n}{K_n}, \quad \tilde{h} = \frac{h}{H_0}, \quad \tilde{y} = \frac{y}{Y_0}, \quad \tilde{x} = \frac{x}{L}, \quad \tilde{t} = \frac{t}{T}, \quad \theta = \frac{t}{\chi T},$$

where K_n is the carrying capacity of the normal cells, C_0 is the reference carrying capacity of the cancer cells, H_0 and Y_0 are the reference concentrations of extracellular and intracellular protons, L is the reference length scale and T is the reference time unit. As the processes on the subcellular scale are much faster than those on the macroscale, $\theta = \frac{\tilde{t}}{\chi}$ with some $\chi \in (0,1)$ represents the time on the microscale.
Using these variables and (2.6), we transform (2.3) to the nondimensionalized system

$$\begin{cases} \partial_t c = \nabla\cdot\left(\frac{D_c}{1+cn}\nabla c\right) - \nabla\cdot\left(\frac{Mc}{1+ch}\nabla h\right) + \frac{\kappa_1}{1+y}c\left(1 - \frac{c}{K_c(h(\cdot,t-\tau))} - \eta_1 n\right), \\ \partial_t n = -\delta_n hn + \mu_n n\left(1 - \eta_2\frac{c}{K_c(h(\cdot,t))} - n\right), \\ \partial_t h = D_h\Delta h + \frac{\gamma_h y}{1+y^2+\alpha_h h^2} - \frac{\beta_h h}{1+y^2}, \\ \partial_\theta y = -\frac{\gamma_y y}{1+y^2+\alpha_h h^2} + \frac{\beta_y h}{1+y^2} - \alpha y + \frac{\rho c}{1+c}, \end{cases} \tag{4.1}$$

in $\Omega\times(0,T)$ with $\Omega := (0,1) \subset \mathbb{R}$, where we omit the tildes in variables and constants for the ease of notation.

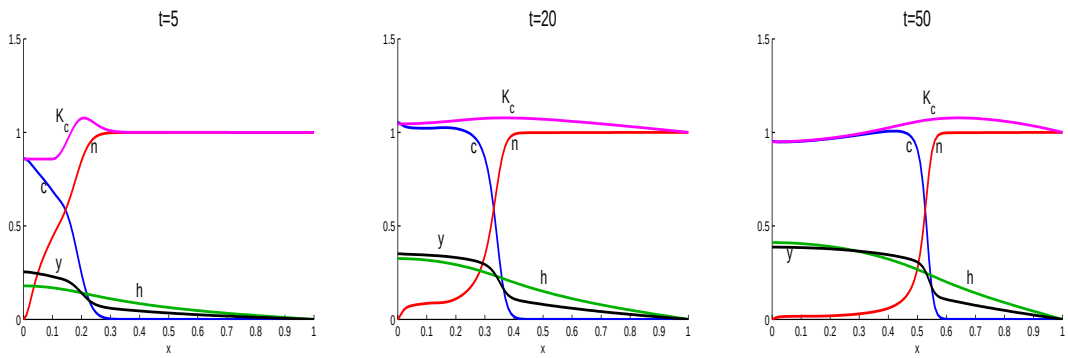
We endow (4.1) with the boundary and initial conditions (2.4)-(2.5) and set

$$c_0(x) := \exp\left(-\frac{x^2}{\varepsilon}\right), \quad n_0(x) := 1 - \exp\left(-\frac{x^2}{\varepsilon}\right), \quad y_0(x) := \xi_y c_0(x),$$
$$h_0(x,t) := \xi_h c_0((x - x_0)_+)$$

for $x \in [0,1]$ and $t \in [-\tau, 0]$, where $(s)_+ := \max\{s, 0\}$ for $s \in \mathbb{R}$. Here the choice of h_0 accounts for an already elevated intratumoral acidosis, which decays towards the tumor border. This is done to include the fact that a too acidic environment is harmful also for cancer cells.

We perform numerical simulations by using an implicit-explicit finite difference scheme as in [30] and choosing the parameters $\tau = 8$, $\chi = 0.01$, $D_c = 2 \cdot 10^{-6}$, $M = 10^{-3}$, $D_h = 0.1$, $\eta_1 = 0.35$, $\eta_2 = 0.05$, $\xi_y = 0.3$, $\xi_h = 0.5$ and $x_0 = 0.1$.

We provide some time snapshots for two different choices of the carrying capacity K_c of the cancer cells. First, we choose $K_c(h) = \frac{1+bh}{1+dh^2}$ with $d > 0$ so that a too acidic environment of the tumor causes a smaller carrying capacity, which leads to a decrease in the original tumor (see Figure 1). In contrast to this, for $K_c(h) = 1 + bh$ the original tumor infers enhanced growth, but does not seem to affect the invasion speed (see Figure 2). The classical choice of a constant carrying capacity (see Figure 3) does not allow the tumor to adapt its growth to the environmental acidity.

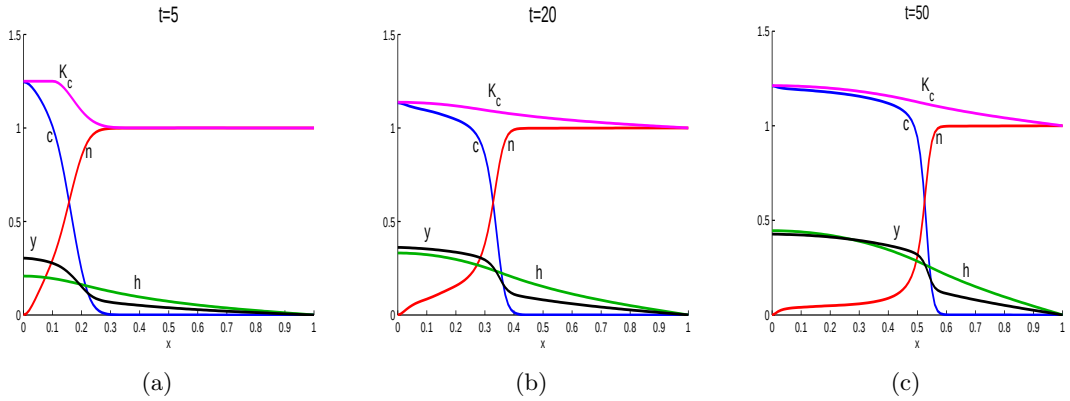


(a) (b) (c)

Figure 1: Evolution of tumor cell (blue) and normal cell densities (red), concentrations of extracellular (green) and intracellular protons (black), and carrying capacity $K_c(h(t-\tau))$ of cancer cells (purple) with $K_c(h) = \frac{1+h}{1+3h^2}$ for model (4.1).

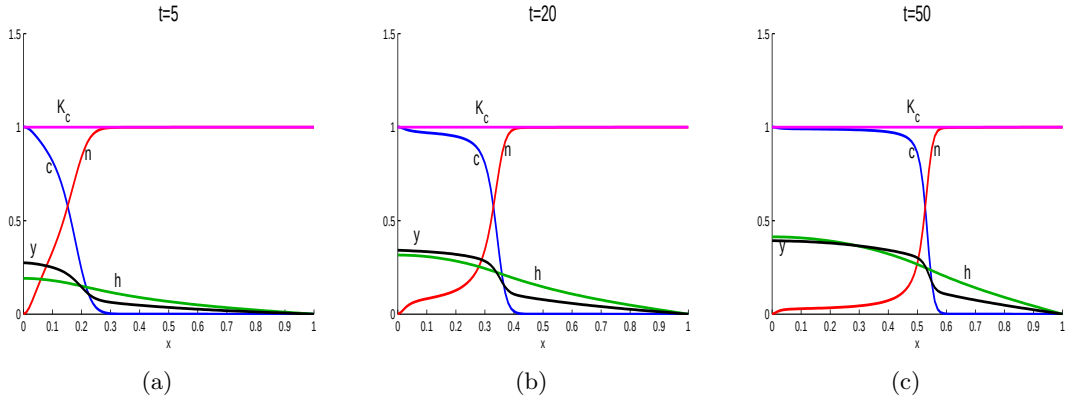
5 Discussion

In this work we proposed a multiscale model for acid-mediated tumor invasion which assigns more importance to the intracellular proton dynamics on the microscale leading to the behavior of the interacting normal and cancer cell populations on the macroscale. The coupling between the two scales is realized through the spatio-temporal evolution of the extracellular protons, which are controlled by and influence the dynamics of the processes taking place both on the microscale and on the macroscale. Moreover, we account for pH-taxis, which characterizes the tactic behavior of tumor cells in response to an extracellular pH gradient, a feature which was only lately proposed in the context of cancer invasion



(a) (b) (c)

Figure 2: Evolution of tumor cell (blue) and normal cell densities (red), concentrations of extracellular (green) and intracellular protons (black) and carrying capacity $K_c(h(t-\tau))$ of cancer cells (purple) with $K_c(h) = 1 + \frac{h}{2}$ for model (4.1).



(a) (b) (c)

Figure 3: Evolution of tumor cell (blue) and normal cell densities (red), concentrations of extracellular (green) and intracellular protons (black) and carrying capacity K_c of cancer cells (purple) with $K_c = 1$ for model (4.1).

[2, 31]. The model was shown to be well posed in the weak sense; the result holds even for a more general case than the concrete situation described in Section 2. The global boundedness of the solution remains, however, open (unless for supplementary assumptions, see Remark 3.7). Numerical simulations illustrate the behavior of the solution as predicted by our model. Thereby, the choice of the carrying capacity as a (delayed) function of the extracellular proton concentration was shown to be relevant: as expected, a larger carrying capacity will enhance tumor growth (though it seems to hardly have an effect on the invasion speed, but proving this mathematically is still an open issue). This would endorse the therapeutical approach aiming to reduce the acidity in the tumor environment to control the neoplasm development [13, 32].

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